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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/148,012	09/04/98	KRIEGER M	MIT7150CIP(2

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EXAMINER	
LANDSMAN, R	
ART UNIT	PAPER NUMBER
1647	12

DATE MAILED: 04/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/148,012	Applicant(s) KRIEGER, MONTY	
	Examiner Robert Landsman	Art Unit 1647	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

1. Formal Matters

A. Amendment B, filed 1/5/01, has been entered into the record.

B. Claims 1-16 are pending in the application.

C. All 35 USC Statutes not found in this Office Action can be found, cited in full, in a previous Office Action.

Withdrawn Objections

A. The objection of Figure 1 has been withdrawn since the Formal Drawings have been submitted which use capital letters.

Withdrawn Rejections

1. Claim Rejections - 35 USC § 102

A. The rejections under 35 USC 102 over (1) Spona et al., (2) Bajetta et al., (3) Cirkel et al. (4) and Whitcroft and Stevenson have been withdrawn since none of these references teach that the compounds used specifically increase SR-BI expression or directly inhibit SR-BI.

Maintained Rejections

1. Claim Rejections - 35 USC § 102

A. The rejection of claims 1-7, 15 and 16 remain rejected over Rigotti et al. for the reasons already of record on page 3 of the Office Action dated 9/11/00. Applicants argue that. Applicants argue that the claims are drawn to a method of treatment requiring at least two elements not shown in the prior art: (a)

the treatment of individuals in need of alteration of the production of reproductive hormones for the treatment of disorders in which the levels of the reproductive hormones are involved (b) by specifically altering SR-BI expression. Applicants further argue that the claim language excludes the general treatment with estrogen.

Applicants' arguments have been considered, but are not deemed persuasive. First, Rigotti et al. teach in the fist two sentences of the right column of page 183, under "Regulation of scavenger receptor BI expression in vivo" that the expression of SR-BI is linked with steroidogenesis. Since reproductive hormones are known to be derived from steroids, one of ordinary skill in the art would immediately envision that it would be possible to regulate the production of these reproductive hormones by altering levels of SR-BI, which is involved in steroidogenesis.

In addition, regarding the term "selectively," the claims can still read on estrogen. While Applicants have stated that estrogen is associated with a number of side effects and that treatment is more preferably achieved through other agents (page 11, lines 2-4 of the specification), it is still not clear that these side effects are not mediated through SR-BI pathways. Furthermore, even if this were not shown to be the case, estrogen still selectively modulates expression of SR-BI, since this is one of the effects that estrogen has "selected" though it may bind other receptors and have other effects besides those on SR-BI and steroidogenesis.

2. Claim Rejections - 35 USC § 112, first paragraph – scope of enablement

A. Claims 1-16 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 7-8 of the Office Action dated 9/11/00. Applicants argue that the legal standard for enablement under 35 USC 112, first paragraph, is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue

experimentation. Applicants have also argued that the Examiner has consistently relied on conclusory statements without putting forth specific reasons describing why the claims are not enabled.

The Examiner has rejected these claims since, while Applicants, on page 10 of the response dated 1/5/01, provide numerous examples of *classes* of compounds which can be used in the present invention, such as antisense oligonucleotides, small organic molecules or soluble SR-BI proteins. However, Applicants have not enabled one of ordinary skill in the art to make specific compounds in these classes. The breadth of the claims is extensive since Applicants are claiming all compounds in all of these classes without describing, or providing any guidance as to what specific molecules can be used in the present invention. Applicants cannot simply claim all small organic molecules or soluble SR-BI proteins and fragments which have the desired effect, since, not only are they not in possession of a representative number of these compounds, but they have not taught one of ordinary skill in the art how to produce, for example, all small organic molecules, or protein fragments which can modulate steroid production.

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very

different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to make the claimed polypeptides.

In addition, picking and choosing the target region for the oligo has proven to be unpredictable. Roush (Science 276:1192-1193) states "For some reason, antisense oligos bind to some sequences with much greater affinity that others" and "randlomly making antisense oligos gives random results, and when it works it's luck." (page 1193, column 1).

Therefore, Applicants have only provided specific examples using estrogen and anti-SR-BI antibodies. Applicants state, however, that estrogen does not meet the limitations of the claims.

In summary, due to the excessive breadth of the claims regarding all small organic molecules, protein fragments and antisense as well as the minimal guidance and working examples of how to make these molecules, along with the unpredictability to one of ordinary skill in the art how to make these compounds, the Examiner maintains that there is inadequate written description which leads to a lack of enablement to practice the invention as claimed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 305-7245. The examiner can normally be reached on Monday - Thursday from 8:00 AM to 4:30 PM (Eastern time) and on alternate Fridays from 8:00 AM to 4:30 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 09, 2001

Gary L. Kunz

GARY L. KUNZ
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